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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,751	01/04/2001	Pnina Fishman	2786-0142 P	4072

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EXAMINER	
LEWIS, PATRICK T	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 06/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,751	FISHMAN, PNINA	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42 and 44-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,42,44-64 and 67-78* is/are rejected.

7)☒ Claim(s) *65,66,79 and 80* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *05202005*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II (claims 41-42 and 44-80) in the reply filed on March 9, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's Response Dated March 9, 2005 (including responses dated January 12, 2004; July 21, 2004; November 22, 2004)

2. In the Response filed March 9, 2005, claims 1-40 and 43 were canceled. Claims 41-42 and 44-80 are pending. An action on the merits of claims 41-42 and 44-80 is contained herein below.

3. The rejection of claims 10-12, 15-18, 20-21 and 41-56 under 35 U.S.C. 112, first paragraph, has been rendered moot in view of applicant's amendment dated March 9, 2005.

4. The rejection of claims 15, 46 and 53 under 35 U.S.C. 112, second paragraph, has been rendered moot in view of applicant's amendment dated March 9, 2005.

5. The rejection of claims 10-11, 15-18, 20 and 43 under 35 U.S.C. 102(b) as being anticipated by Kohno et al., Biochemical and Biophysical Research Communications, (1996), Vol. 219, pages 904-910 (Kohno) has been rendered moot in view of applicant's amendment dated March 9, 2005.

6. The rejection of claims 41-42 and 46-49 under 35 U.S.C. 102(b) as being anticipated by Kohno et al., Biochemical and Biophysical Research Communications, (1996), Vol. 219, pages 904-910 (Kohno) is maintained for the reasons of record set forth in the Office Action dated July 10, 2003.

7. The rejection of claims 10-11, 15-16, 20 and 43 under 35 U.S.C. 102(b) as being anticipated by Mittelman et al. Annals New York Academy of Sciences, (1975), Vol. 225, pages 225-234 (Mittelman) has been rendered moot in view of applicant's amendment dated March 9, 2005.

The declarations under 37 CFR 1.132 filed March 9, 2005 are sufficient to overcome the rejection of claims 41-42 and 46-47 based upon the rejection over Mittelman under 35 U.S.C. 102(b).

8. The rejection of claims 10-12, 15-18, 20-21 and 43 under 35 U.S.C. 103(a) as being unpatentable over Kohno in view of Jacobson et al. US 5,688,774 (Jacobson) has been rendered moot in view of applicant's amendment dated March 9, 2005.

9. The rejection of claims 41-42 and 44-49 under 35 U.S.C. 103(a) as being unpatentable over Kohno in view of Jacobson et al. US 5,688,774 (Jacobson) is maintained for the reasons of record set forth in the Office Action dated July 10, 2003.

10. The rejection of claims 10-12, 15-18, 20-21 and 43 under 35 U.S.C. 103(a) as being unpatentable over Kohno and Can-Fite Technologies LTD WO 99/02143 (Can-Fite) in view of Jacobson et al. US 5,688,774 (Jacobson) has been rendered moot in view of applicant's amendment dated March 9, 2005.

11. The rejection of claims 41-42 and 44-56 under 35 U.S.C. 103(a) as being unpatentable over Kohno and Can-Fite Technologies LTD WO 99/02143 (Can-Fite) in view of Jacobson et al. US 5,688,774 (Jacobson) is maintained for the reasons of record set forth in the Office Action dated July 10, 2003.

Rejections of Record Set Forth in the Office Action Dated July 10, 2003

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 41-42 and 46-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Kohno et al., Biochemical and Biophysical Research Communications, (1996), Vol. 219, pages 904-910 (Kohno).

Applicant's arguments filed March 9, 2005 have been fully considered but they are not persuasive. Applicant argues that the nanomolar (nM) concentration ranges of IB-MECA and Cl-IB-MECA administered by Kohno are too high to achieve the claimed selectivity and act through different mechanisms and thus do not induce their action primarily through the A_3 adenosine receptor. The declaration under 37 CFR 1.132 filed January 12, 2004 is insufficient to overcome the rejection of claims 41-42 and 46-49 under 35 U.S.C. 102(b) as being anticipated by Kohno as set forth in the last Office Action.

Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. In construing process claims and references, it is the identity of manipulative operations which leads to finding of anticipation. In the instant case, it

does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Kohno teaches that ADO regulates a variety of physiological effects on numerous cell types through activation of membrane-bound adenosine receptors. These have been classified into four distinct subtypes, A_1, A_{2a}, A_{2b} and A_3. Kohno teaches that IB-MECA and Cl-IB-MECA are selective A_3 receptor agonist at concentrations ≤ 30 μM.

14. Claims 41-42 and 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno in view of Jacobson et al. US 5,688,774 (Jacobson).

Applicant's arguments filed March 9, 2005 have been fully considered but they are not persuasive. Applicant argues that the nanomolar (nM) concentration ranges of IB-MECA and Cl-IB-MECA administered by Kohno are too high to achieve the claimed selectivity and act through different mechanisms and thus do not induce their action primarily through the A_3 adenosine receptor.

The declaration under 37 CFR 1.132 filed January 12, 2004 is insufficient to overcome the rejection of claims 41-42 and 44-49 under 35 U.S.C. 103(a) as being unpatentable over Kohno in view of Jacobson et al. US 5,688,774 (Jacobson) as set forth in the last Office Action. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. In construing process claims and references, it is the identity of manipulative operations which leads to finding of unpatentability. Kohno teaches that ADO regulates a variety of physiological effects on numerous cell types through activation of membrane-bound adenosine receptors. These have been classified into four distinct subtypes, A_1, A_{2a}, A_{2b} and A_3. Kohno

teaches that IB-MECA and Cl-IB-MECA are selective A_3 receptor agonist at concentrations ≤ 30 μM.

15. Claims 41-42 and 44-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno and Can-Fite Technologies LTD WO 99/02143 (Can-Fite) in view of Jacobson et al. US 5,688,774 (Jacobson).

Applicant's arguments filed March 9, 2005 have been fully considered but they are not persuasive. Applicant argues that the nanomolar (nM) concentration ranges of IB-MECA and Cl-IB-MECA administered by Kohno are too high to achieve the claimed selectivity and act through different mechanisms and thus do not induce their action primarily through the A_3 adenosine receptor.

The declaration under 37 CFR 1.132 filed January 12, 2004 is insufficient to overcome the rejection of claims 41-42 and 44-56 under 35 U.S.C. 103(a) as being unpatentable over Kohno and Can-Fite Technologies LTD WO 99/02143 (Can-Fite) in view of Jacobson et al. US 5,688,774 (Jacobson) as set forth in the last Office Action. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. In construing process claims and references, it is the identity of manipulative operations which leads to finding of unpatentability. Kohno teaches that ADO regulates a variety of physiological effects on numerous cell types through activation of membrane-bound adenosine receptors. These have been classified into four distinct subtypes, A_1, A_{2a}, A_{2b} and A_3. Kohno teaches that IB-MECA and Cl-IB-MECA are selective A_3 receptor agonist at concentrations ≤ 30 μM (see Abstract).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. Claims 57-64 and 67-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno et al., Biochemical and Biophysical Research Communications, (1996), Vol. 219, pages 904-910 (Kohno) and Can-Fite Technologies LTD WO 99/02143 (Can-Fite) in view of Jacobson et al. US 5,688,774 (Jacobson).

Applicant claims the use of various adenosine A3 receptor agonists to treat abnormal cellular proliferation. Further, applicant claims the use of adenosine A3 receptor agonists in combination with a chemotherapeutic drug. Applicant also claims methods to treat cancer by administering an adenosine A3 receptor agonist that also counters the toxic side elects of a chemotherapeutic drug, optionally providing a stronger synergistic effect. Finally, Applicant claims methods wherein the adenosine A3 receptor agonist is administered orally.

Kohno teaches that adenosine A3 receptor agonists, such as IB-MECA and Cl-IB-MECA, induce apoptosis in HL-60 human promyelocytic leukemia cells, and therefor have therapeutic value in the treatment of leukemia.

Kohno does not specifically teach that the adenosine A3 receptor agonists, IB-MECA and Cl-IB-MECA, can be administered orally or in combination with a chemotherapeutic drug. Further, Kohno does not explicitly state that such adenosine A3 receptor agonists would be able to counter the toxic side effects of a chemotherapeutic drug or would have a strong synergistic effect with such chemotherapeutic drug.

CAN-FITE teaches that adenosine has an effect in inducing proliferation of bone marrow cells, resulting in increase in the number of leukocytes and particularly of neutrophils in the peripheral blood, thereby exhibiting a protective effect against some toxic effect of chemotherapeutic drugs. See page 6, lines 6-17. Further, on that same page, lines 28-25, CAN-FITE discloses that the overall effect of adenosine when administered together with a chemotherapeutic drug is an increase in the therapeutic index, namely by reducing the toxic side effects and improving specific activity. CAN-FITE further extrapolates that such an effect can be achieved using agents that interact with the adenosine system. "In addition, as will no doubt be appreciated by the artisan, although the use of adenosine is preferred in accordance with the invention, other nucleosides as well as nucleoside derivatives may potentially be used to obtain qualitatively similar effects to that of adenosine." See page 7, lines 5-29.

Jacobson teaches the use of adenosine A3 receptor agonists in the regulation of CNS, cardiac inflammatory and reproductive functions. See column 3, lines 45-67. Further, Jacobson discloses that the therapeutically effective adenosine A3 receptor agonists can be administered orally (column 10, lines 29-57).

Since Kohno teaches that the adenosine A3 receptor agonists have therapeutic value in the treatment of leukemia, and combination therapies are standard in the art of cancer therapeutics, a skilled artisan would have been motivated and had a reasonable expectation of success for treating leukemia using an adenosine A3 receptor agonist of Kohno in combination with one or more other known chemotherapeutic agent. Further, it would have been obvious to one of ordinary skill in the art that the adenosine derivatives of Kohno could also induce the proliferation of bone marrow cells, resulting in an increase in the number of leukocytes and particularly of neutrophils in the peripheral blood, thereby exhibiting a protective effect against some toxic effect of chemotherapeutic drugs, as per CAN-FITE. Therefore, a skilled artisan would have been motivated and had a reasonable expectation of success for using the adenosine A3 receptor agonists of Kohno to treat cancer with the dual effect of inhibiting proliferation of cancer cells and countering the toxic side effects of chemotherapeutic drug treatment. Finally, it would have been obvious to one of ordinary skill in the art to administer the adenosine A3 receptor agonists of Kohno orally, as Jacobson teaches that such compounds are easily formulated for oral administration.

Conclusion

19. Claims 41-42 and 44-80 are pending. Claims 41-42, 44-64 and 67-78 are rejected. Claims 65-66 and 79-80 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

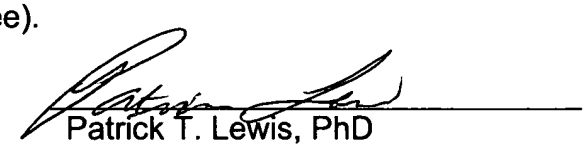
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patrick T. Lewis, PhD
Examiner
Art Unit 1623

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